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Efficacy of preoperative administration of single high dose intravenous tranexamic acid in reducing blood loss in total knee arthroplasty: A prospective clinical study

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ABSTRACT

Objective: The aim of this study was to analyse the effectiveness of single dose of 20 mg/kg intravenous tranexamic acid (TXA), in reducing the blood loss in patients undergoing total knee arthroplasty (TKA).
Material and method: 70 patients (65.5 ± 8.1 years old) that have undergone TKA were divided in two groups. The 20 mg/kg IV TXA was given before the skin incision to one group (study group). On the control group, TKA was performed without TXA. The demographic data, body mass index, amount of bleeding and erythrocyte infusion during the operation, hemoglobin and hematocrit values (preoperative and 48th hour), the amount of drainage after the operation were compared between the groups.
Results: The total amount of bleeding in the study group was 634.03 ± 182.88 ml and 1166.42 ± 295.92 ml in the control group ($p < 0.001$). Perioperative bleeding was 252.01 ± 144.13 ml in the study group and 431.33 ± 209.10 ml in the control group ($p = 0.018$). The drainage after the operation was 311.11 ± 141.64 ml at the 24th hour in the study group, 640.74 ± 279.43 ml at the 24th hour in the control group ($p < 0.001$). The drainage after 24th hour was 97.96 ± 115.86 ml in the study group and 112.96 ± 64.43 ml in the control group ($p = 0.584$).
Conclusion: A high, single dose of TXA intravenously given to the patient prior to the TKA significantly reduces the bleeding during the operation and within the postoperative 24 h. There is no significant change in the bleeding amount after the 24th hour following the operation.

Introduction

Total knee arthroplasty (TKA) is a method that has proven to be effective in treatment of severe knee arthrosis. Although it is a successful treatment, arthroplasty may cause certain adverse events. For example, 500–1500 cc of blood loss has been reported following the procedure.[1–4] The blood loss may cause prolonged physical treatment, increased infection rates, prolonged length of hospital stay, and side effects caused by the need for transfusion.[5–7]

The literature describes a number of modalities which have been reported to produce a significant reduction in the volume of blood loss.[1–6,8,9] Tranexamic acid (TXA), intravenous (IV) or topical, is one such modality,[7,8,10–14] with both modes of administration having been shown effective.[3] TXA produces its hemostatic effect through plasminogen activation and by creating an inhibitory effect on active plasmin. The effect of TXA on blood loss lasts for 7–8 h in serum and for a longer period in tissue.[8,10,14,15]

In the present study, the effects of 20 mg/kg IV TXA on blood loss during and after unilateral TKA when administered preoperatively were reviewed prospectively.

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Patients and methods

Our study was performed with the approval of the institutional ethics committee. Seventy patients diagnosed with ASA (American Society of Anesthesiologists) grade 1–3 gonarthrosis who were scheduled for knee arthroplasty were included in this prospective observational review. Exclusion criteria for the study were prolonged use of anticoagulant medication, chronic renal impairment, previous history of deep venous thrombosis (DVT) or pulmonary embolism (PE), having undergone revision surgery and simultaneous bilateral knee arthroplasty, having thrombocyte level below 150,000 and INR level above 1.4, and having rheumatic or hematological diseases.

The patients included in the study were divided into 2 groups. The study group received 20 mg/kg IV TXA 20 min before the skin incision, with use of a tourniquet only during the cementation phase. The control group received knee arthroplasty without TXA. All patients received neuroaxial anesthesia (spinal or combined spinal epidural). Knee arthroplasty was performed with standard medial parapatellar incision, with use of an intramedullary guide for the femur and extramedullary guide for the tibia section. The same type of knee implant protecting the posterior cruciate ligaments was used on all patients. Prophylactic treatment with 2 g cefazolin was initiated 30 min prior to the operation and continued for 24 h as 1 g administered 4 times/day. The patients were mobilized with partial weights and crutches within the first 24 h after the operation. The drainage in patients was recorded at the 24th and 48th hour. One dose of 0.4 ml (4000 IU) enoxaparin (Clexane, 4000 anti-Xa IU/0.4 ml, Sanofi-Aventis, Gentilly, France) was given 12 h prior to the surgery subcutaneously as the standard application. At the time of discharge, the patients were given 100 mg/day acetylsalicylic acid. The threshold for allogeneic blood replacement was considered as 7 g/dl, with the exception of patients with serious conditions of comorbidities or cardiac diseases (such as coronary artery disease, cerebrovascular events, or cardiac insufficiency) when the threshold was changed to 10 g/dl. Patients received 1 unit of allogeneic erythrocytes when hemoglobin values dropped below these thresholds. The volume of blood lost intraoperatively was calculated from the volume of blood in the aspirator and irrigation fluid, plus the volume of blood on the gauze pad (calculated by weighing the gauze pads).

Patients' demographic data, body mass indexes, volume of intraoperative blood loss and erythrocyte infusion, hemoglobin and hematocrit values preoperatively and 48 h postoperatively, and the volume of blood drainage during the first 24 and 48 (total value from first 24-h period, plus additional volume measured in second 24-h period) h after the operation were reviewed.

Student's t-test was used for evaluating quantitative data with normal distribution and Mann–Whitney U test for data not having normal distribution. Chi-square test was used to evaluate qualitative data. Statistical significance was established at $p < 0.05$. SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Study patients were divided into 2 groups of 35 patients (mean age: 64.5 ± 8.1 years). There were no significant differences in terms of patient demographic data. Body mass index was 32.8 ± 0.6 in the study group and 35 ± 5.9 in the control group ($p = 0.165$).

The results of the study showed that the total volume of blood loss was significantly reduced in the study group that received TXA (634.03 ± 182.88 ml) compared to the control group (1166.42 ± 295.92 ml) ($p < 0.001$).

The volume of blood loss during the operation was also significantly reduced in the study group (252.01 ± 144.13 ml) compared to the control group (431.33 ± 209.10 ml) ($p = 0.018$). Similarly, the allogeneic transfusion level in the study group was significantly lower than in the control group (Table 2).

Hemoglobin values both pre- and postoperatively were not significantly different between the study and control groups.

The total volume of blood loss postoperatively was significantly lower in the study group compared to the control group at both the 24th hour and 48th hour time points: the study group was 311.11 ± 141.64 ml at the 24th hour and 392.03 ± 160.42 ml at the 48th hour, while the control group 640.74 ± 279.43 ml at the 24th hour and 746.43 ± 271.80 ml at the 48th hour ($p < 0.001$ for both comparisons). Drainage after the 24th hour was 97.96 ± 115.86 ml in the study group that received TAX and 112.96 ± 64.43 ml in the control group, with no significant difference between the groups ($p = 0.584$) (Table 1).

One patient in the study group of TXA treatment developed an adverse event of PE in the third week postoperatively, which was medically treated ($p = 0.314$).

Discussion

The benefit of TXA use as an antifibrinolytic agent to reduce blood loss after knee arthroplasty was first described by Hippala et al.[12] TXA has been generally used in dental surgery, cardiac surgery, and the treatment of hemophilia disease as an antihemorrhagic agent but is now beginning to be used in arthroplasty surgery.

A number of publications indicate significant reduction in the volume of blood loss.[7,8,10–12,14] The literature states the blood loss volumes as ranging between 360 ml and 800 ml. In the present study, the average volume of blood loss in the study group was 634.03 ± 182.88 ml, which is in accordance with the volumes stated in the literature and was significantly lower than the blood loss in the control group, which did not receive TXA (1166.42 ± 295.92 ml) ($p < 0.001$). The volume of blood loss in the study group was close to the upper limit stated in the literature, despite the TXA treatment, because tourniquet was not used during the operation; additionally, perioperative blood loss was included in the total volume of blood loss. The volume of postoperative blood loss was 392.03 ± 160.65 ml.

Table 1
Postoperative blood loss data.

	TXA group (n = 35)	Control group (n = 35)	[a]p-value
Drains 0–24 h (ml)	311.11 ± 141.64	640.74 ± 279.435	<0.001*
Drains 24–48 h (ml)	97.96 ± 115.86	112.96 ± 64.43	0.584
Total volume of drains (ml)	392.03 ± 160.65	746.43 ± 271.80	<0.001*
Total volume of blood loss (ml)	634.03 ± 182.88	1166.42 ± 295.92	<0.001*

*$p < 0.05$ considered significant.
[a] Student's t-test.

Table 2
Perioperative blood loss data.

	TXA group (n = 35)	Control group (n = 35)	p-value
Perioperative blood loss (ml)	252.01 ± 144.13	431.33 ± 209.10	[a]0.018*
Perioperative transfusion (unit)	0.74 ± 0.44	1.02 ± 0.38	[a]0.006*

*p < 0.05 considered significant.
[a] Student's t-test.

Nonetheless, there is no consensus about the starting time, methods, or volume of usage of TXA.[14,16–19] Multiple doses or topical use combined with IV administration is claimed to be more successful than single-dose usage.[17,18] Hourlier et al showed in their study that the single-dose TXA method is as effective as the multiple dose method.[16] They stated that the previous studies failed to show the efficacy of single-dose treatment because they usually used low doses and that the efficient dose should be 30 mg/kg.[16] TXA begins to take effect within 15 min of administration and remains effective for 7–8 h in serum and up to 17 h in tissue. The fact that the majority of blood loss occurs within the first 5 h after the operation[9,20] indicates that preoperative IV TXA treatment has a sufficiently fast effect on blood loss. In our study, the volume of blood loss experienced during the first 24 h postoperatively was 311.11 ± 141.64 ml in the study group and 640.74 ± 279.435 ml in the control group (p < 0.001). However, there were no significant differences between the volumes of blood loss in the 2 groups after the 24th hour (p = 0.58). Treatment with a high dose of TXA 20 min before the skin incision creates a statistically significant reduction in blood loss volume both during and after the operation compared to standard treatment.

The volume of blood loss during the operation was significantly reduced with TXA treatment prior to the operation compared to the non-TXA group (p = 0.018). The literature confirms the statistically significant reduction in blood loss in a meta-analysis.[19] These differences can be explained with the dose used and timing of the treatment.

The literature indicates that bolus blood loss occurs despite TXA treatment in patients subject to tourniquet use.[18] The authors recommend opening of the drain 1 h after the operation to avoid bolus blood loss. Our use of tourniquet only during cementation helped us avoid bolus blood loss and permitted hemostasis in our study. Furthermore, since TXA was applied immediately before the operation, it was effective, and bolus blood loss did not occur in our study.

The literature generally states that use of TXA to control blood loss does not create the risk of DVT or PE and that TXA treatment is safe.[16,21] Zhang et al, however, found in their meta-analysis study that 5 of their patients had PE, 2 of whom were among the patients who had received TXA.[14] In our study, PE was diagnosed in 1 of 30 patients, who was treated with anticoagulant therapy. This single occurrence was not significant (p = 0.356). One restriction of the present study was that there was no standard protocol for monitoring of patients with venography in order to diagnose possible DVT.

The preoperative use of single and high dose of TXA on patients undergoing TKA significantly reduces the volume of blood loss during the operation and in the first 24 h postoperatively. There was no significant difference in blood loss volume after the 24th hour, a period in which little blood loss is typically observed.

Conflict of interest

None declared.

References

1. Morais S, Ortega-Andreu M, Rodriguez-Merchan EC, et al. Blood transfusion after primary total knee arthroplasty can be significantly minimised through a multimodal blood-loss prevention approach. *Int Orthop*. 2014;38:347–354.
2. Ma J, Huang Z, Shen B, Pei F. Blood management of staged bilateral total knee arthroplasty in a single hospitalization period. *J Orthop Surg Res*. 2014;9:116.
3. Keska R, Paradowski TP, Witonski D. Outcome in primary cemented total knee arthroplasty with or without drain: a prospective comparative study. *Indian J Orthop*. 2014;48:404–409.
4. Sasanuma H, Sekiya H, Takatoku K, Takada H, Sugimoto N, Hoshino Y. Efficient strategy for controlling postoperative hemorrhage in total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2011;19:921–925.
5. Shaieb MD, Watson BN, Atkinson RE. Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis. *J Arthroplast*. 1999;14:432–438.
6. Liu F, Chu X, Huang J, Tian J, Hua J, Tong P. Administration of enoxaparin 24 h after total knee arthroplasty: safer for bleeding and equally effective for deep venous thrombosis prevention. *Arch Orthop Trauma Surg*. 2014;134:679–683.
7. Goodnough LT. Risks of blood transfusion. *Anesthesiol Clin N Am*. 2005;23:241–252.
8. Orpen NM, Little C, Walker G, Crawfurd EJ. Tranexamic acid reduces early postoperative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. *Knee*. 2006 Mar;13:106–110. Epub 2006 Feb 17.
9. Jung WH, Chun CW, Lee JH, Ha JH, Kim JH, Jeong JH. No difference in total blood loss, haemoglobin and haematocrit between continues and intermittent wound drainage after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2013;21:2831–2836.
10. Ishida K, Tsumura N, Kitagawa A, et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. *Int Orthop*. 2011;35:1639–1645.
11. Nielsen RE, Husted H. Tranexamic acid reduces blood loss and the need of blood transfusion after knee arthroplasty. *Ugeskr Laeger*. 2002:14;164:326–329.
12. Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth*. 1995;74:534–537.
13. Moskal JT, Harris RN, Capps SG. Transfusion cost savings with tranexamic acid in primary total knee arthroplasty from 2009 to 2012. *J Arthroplast*. 2015 Mar;30:365–368.
14. Wu Q, Zhang HA, Liu SL, Meng T, Zhou X, Wang P. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2015 Apr;25:525–541.
15. Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. *Can J Anaesth*. 1992;39:353–365.
16. Hourlier H, Reina N, Fennema P. Single dose intravenous tranexamic acid as effective as continuous infusion in primary total knee arthroplasty: a randomised clinical trial. *Arch Orthop Trauma Surg*. 2015;135:465–471.
17. Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar RP. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res*. 2012;470:2605.
18. Lin Sung-Yen, Chen Chung-Hwan, Fu Yin-Chih, Huang Peng-Ju, Chang Je-Ken, Huang Hsuan-Ti. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. *J Arthroplast*. 2015;30:776–780.
19. Zhang H, Chen J, Chen F, Que W. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta- analysis. *Knee Surg Sports Traumatol Arthrosc*. 2012;20:1742–1752.
20. Senthil Kumar G, Von Arx OA, Pozo JL. Rate of blood loss over 48 hours following total knee replacement. *Knee*. 2005;12:307–309.
21. Gillette BP, DeSimone LJ, Trousdale RT, Pagnano MW, Sierra RJ. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res*. 2013;471:150–154.